Annex I

List of the names, pharmaceutical forms, strengths of the medicinal products, routes of administration, marketing authorisation holders in the member states

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Czech Republic	sanofi-aventis, s.r.o. Evropská 846/176a 160 00 Praha 6 - Vokovice Czech Republic	MUSCORIL CPS	4mg	Capsule, hard	Oral use
Czech Republic	sanofi-aventis, s.r.o. Evropská 846/176a 160 00 Praha 6 - Vokovice Czech Republic	MUSCORIL INJ	4mg/2ml	Solution for injection	Intramuscular use
France	Actavis Group PTC ehf Reykjavikurvegur 76-78 220 Hafnarfjordur Iceland	THIOCOLCHICOSIDE ACTAVIS 4 mg, comprimé	4mg	Tablet	Oral use
France	Alter 3, avenue de la Baltique ZI de Courtaboeuf 91140 Villebon Sur Yvette France	THIOCOLCHICOSIDE ALTER 4 mg, comprimé	4mg	Tablet	Oral use
France	Arrow Generiques 26, avenue Tony Garnier 69007 Lyon France	THIOCOLCHICOSIDE ARROW 4 mg, comprimé	4mg	Tablet	Oral use
France	Biogaran 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE ALMUS 4 mg, comprimé	4mg	Tablet	Oral use

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France	Biogaran 15, boulevard Charles de Gaulle 92700 Colombes France	THIOCOLCHICOSIDE BIOGARAN 4 mg, comprimé	4mg	Tablet	Oral use
France	Cristers 22 quai Gallieni 92150 Suresnes France	THIOCOLCHICOSIDE CRISTERS 4 mg, comprimé	4mg	Tablet	Oral use
France	DAIICHI SANKYO France SAS Immeuble le Corosa 1, rue Eugene et Armand Peugeot 92508 Rueil Malmaison France	MIOREL 4 mg, gélule	4mg	Tablet	Oral use
France	DAIICHI SANKYO France SAS Immeuble le Corosa 1, rue Eugene et Armand Peugeot 92508 Rueil Malmaison France	MIOREL 4 mg/2 ml, solution injectable (IM) en ampoule	4mg/2ml	Solution for injection	Intramuscular use
France	Eg Labo - Laboratoires Eurogenerics "Le Quintet" - bâtiment A 12, rue Danjou 92517 Boulogne Billancourt Cedex France	THIOCOLCHICOSIDE EG 4 mg, comprimé sécable	4mg	Breakable tablet	Oral use

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France	Laboratoires Genevrier S.A. 280, rue de Goa Z.I. Les Trois Moulins Parc de Sophia Antipolis 06600 Antibes France	MYOPLEGE 4 mg, gélule	4mg	Capsule, hard	Oral use
France	Laboratoires Pharmy II 26, rue des Gaudines 78100 Saint-Germain-en-Laye France	COLTHIOZID 4 mg/2 ml, solution injectable	4mg/2ml	Solution for injection	Intramuscular use
France	Mylan SAS 117, allée des Parcs 69800 Saint-Priest France	THIOCOLCHICOSIDE MYLAN 4 mg, comprimé	4mg	Tablet	Oral use
France	Ratiopharm(Germany) Graf Arco Strasse 3 89079 Ulm Germany	THIOCOLCHICOSIDE RATIOPHARM 4 mg, comprimé sécable	4mg	Breakable tablet	Oral use
France	Sandoz 49, avenue Georges Pompidou 92300 Levallois-Perret France	THIOCOLCHICOSIDE SANDOZ 4 mg, comprimé	4mg	Tablet	Oral use
France	Sanofi Aventis France 1-13, boulevard Romain Rolland 75014 Paris France	COLTRAMYL 4 mg, comprimé	4mg	Tablet	Oral use

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
France	Sanofi Aventis France 1-13, boulevard Romain Rolland 75014 Paris France	COLTRAMYL 4 mg/2 ml, solution injectable IM en ampoule	4mg/2ml	Solution for injection	Intramuscular use
France	Sanofi Aventis France 1-13, boulevard Romain Rolland 75014 Paris France	THIOCOLCHICOSIDE ZENTIVA 4 mg, comprimé	4mg	Tablet	Oral use
France	Teva Sante 110, Esplanade du Général de Gaulle 92931 Paris La Défense Cedex France	THIOCOLCHICOSIDE TEVA 4 mg, comprimé	4mg	Tablet	Oral use
Greece	Iasis Pharmaceuticals Hellas AEBE, 137 Fylis Av. 13451 Kamatero,Athens Greece	RELIEF	4mg	Capsule	Oral use
Greece	Iasis Pharmaceuticals Hellas AEBE, 137 Fylis Av. 13451 Kamatero,Athens Greece	RELIEF	4mg/2ml	Solution for injection	Intramuscular use
Greece	Sanofi-Aventis AEBE Syngrou Av. 348 Building A' 17674, Kallithea, Athens Greece	MUSCO-RIL	4mg/2ml	Solution for injection	Intramuscular use

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Greece	Sanofi-Aventis AEBE Syngrou Av. 348 Building A' 17674, Kallithea, Athens Greece	MUSCO-RIL	4mg	Capsule	Oral use
Hungary	Sanofi-Aventis Magyarország Kereskedelmi és Szolgáltató Kft. Tó u. 1-5 Budapest 1045 Hungary	Muscoril	4mg	Capsule, hard	Oral use
Hungary	Sanofi-Aventis Magyarország Kereskedelmi és Szolgáltató Kft. Tó u. 1-5 Budapest 1045 Hungary	Muscoril	4mg	Solution for injection	Intramuscular use
Italy	Angenerico S.P.A. Via Nocera Umbra, 75 00181 Rome Italy	TIOCOLCHICOSIDE ANGENERICO	4mg/2ml	Solution for injection	Intramuscular use
Italy	Crinos S.P.A. Via Pavia, 6 20136 Milan Italy	DECONTRIL	4mg/2ml	Solution for injection	Intramuscular use
Italy	Doc Generici S.R.L. Via Manunzio, 7 20124 Milan Italy	TIOCOLCHICOSIDE	4mg/2ml	Solution for injection	Intramuscular use

Member State (in EEA)	Marketing Authorisation Holder	Invented name Name	Strength	Pharmaceutical Form	Route of administration
Italy	Dompe' S.P.A. Via Campo di Pile S.N.C. 67100 L'Aquila Italy	MIOTENS	4mg/2ml	Solution for injection	Intramuscular use
Italy	EG S.P.A. Via Domenico Scarlatti, 31 20124 Milan Italy	TIOCOLCHICOSIDE EG	4mg/2ml	Solution for injection	Intramuscular use
Italy	Epifarma S.R.L. Via San Rocco, 6 85033Episcopia (Potenza) Italy	MUSCOFLEX	4mg/2ml	Solution for injection	Intramuscular use
Italy	Farmaceutici Caber S.P.A. Viale Citta' D'Europa, 681 Rome Italy	TIOSIDE	4mg/2ml	Solution for injection	Intramuscular use
Italy	Farmaceutici Caber S.P.A. Viale Citta' D'Europa, 681 Rome Italy	TIOSIDE	4mg	Capsule, hard	Oral use
Italy	Germed Pharma S.P.A. Via Cantu', 11 20092 Cinisello Balsamo Milan Italy	TIOCOLCHICOSIDE GERMED	4mg/2ml	Solution for injection	Intramuscular use

Member State (in EEA)	Marketing Authorisation Holder	Invented name Name	Strength	Pharmaceutical Form	Route of administration
Italy	Laboratorio Farmaceutico C.T. S.R.L. Strada Solaro 75/7 Sanremo (IM) Italy	SCIOMIR	4mg/2ml	Solution for injection	Intramuscular use
Italy	MDM S.P.A. Viale Papiniano, 22/B 20123 Milan Italy	STRIALISIN	4mg/2ml	Solution for injection	Intramuscular use
Italy	Mylan S.P.A. Via Vittor Pisani, 20 20124 Milan Italy	TIOCOLCHICOSIDE MYLAN GENERICS	4mg/2ml	Solution for injection	Intramuscular use
Italy	Sandoz S.P.A. Largo Umberto Boccioni, 1 21040 Origgio (Varese) Italy	TIOCOLCHICOSIDE	4mg/2ml	Solution for injection	Intramuscular use
Italy	Sanofi Aventis S.P.A. Viale Luigi Bodio, 37/B 20158 Milan Italy	MUSCORIL	4mg/2ml	Solution for injection	Intramuscular use
Italy	Sanofi Aventis S.P.A. Viale Luigi Bodio, 37/B 20158 Milan Italy	MUSCORIL	4mg	Capsule, hard	Oral use

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Sanofi Aventis S.P.A. Viale Luigi Bodio, 37/B 20158 Milan Italy	MUSCORIL	8mg	Capsule, hard	Oral use
Italy	Sanofi Aventis S.P.A. Viale Luigi Bodio, 37/B 20158 Milan Italy	MUSCORIL	8mg	Orodispersible tablet	Oral use
Italy	SPA - Societa' Prodotti Antibiotici S.P.A. Via Biella, 8 20143 Milan Italy	MIOREXIL	4mg/2ml	Solution for injection	Intramuscular use
Italy	Union Health S.R.L. Via Adige, 5 66020 San Giovanni Teatino (Chieti) Italy	TIOCOLCHICOSIDE UNION HEALTH	4mg/2ml	Solution for injection	Intramuscular use
Italy	Wellington Street Development Pharma Limited 47, Oaklands Drive Rathgar Dublin 6 Ireland	TERASIDE	4mg/2ml	Solution for injection	Intramuscular use
Italy	Zentiva Italia S.R.L. Viale Luigi Bodio, 37/B 20158 Milan Italy	TIOCOLCHICOSIDE ZENTIVA	4mg	Capsule, hard	Oral use

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Zentiva Italia S.R.L. Viale Luigi Bodio, 37/B 20158 Milan Italy	TIOCOLCHICOSIDE ZENTIVA	4mg/2ml	Solution for injection	Intramuscular use
Malta	Sanofi-Aventis Malta Ltd Floor 3, Charles de Giorgio Buildings Triq Kan. K. Pirotta Birkirkara, BKR 1114, Malta	Coltramyl	4mg	Tablet	Oral use
Portugal	Acarpia Servicos Farmaceuticos Lda Rua dos Murcas, 88 9000 Funchal - Madeira Portugal	MOVERIL	4mg/2ml	Solution for injection	Intramuscular use
Portugal	Angelini Farmacêutica, Lda. Rua João Chagas, 53 Piso 3 1499-040 Cruz Quebrada - Dafundo Portugal	Adalgur N	2mg 500mg	Tablet	Oral use
Portugal	Generis Farmacêutica, S.A. Rua João de Deus, 19 2700-487 Amadora Portugal	Tiocolquicosido Arrowblue	4mg	Tablet	Oral use
Portugal	Generis Farmacêutica, S.A. Rua João de Deus, 19 2700-487 Amadora Portugal	Tiocolquicosido Generis	4mg	Tablet	Oral use

Member State (in EEA)	Marketing Authorisation Holder	Invented name Name	Strength	Pharmaceutical Form	Route of administration
Portugal	Korangi - Produtos Farmacêuticos, Lda. Rua de Santa Cruz, Lote 9 2750-063 Cascais Portugal	Coltramyl	4mg	Tablet	Oral use
Portugal	Korangi - Produtos Farmacêuticos, Lda. Rua de Santa Cruz, Lote 9 2750-063 Cascais Portugal	Coltramyl	4mg/2ml	Solution for injection	Intramuscular use
Portugal	Sanofi - Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park Edifício 7 3º Piso 2740-244 Porto Salvo Portugal	Relmus	8mg	Capsule	Oral use
Portugal	Sanofi - Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park Edifício 7 3º Piso 2740-244 Porto Salvo Portugal	Relmus	4mg/2ml	Solution for injection	Intramuscular use

Member State (in EEA)	**Marketing Authorisation Holder**	**Invented name Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	Sanofi - Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park Edifício 7 3º Piso 2740-244 Porto Salvo Portugal	Relmus	4mg	Capsule	Oral use
Portugal	Sanofi - Produtos Farmacêuticos, Lda. Empreendimento Lagoas Park Edifício 7 3º Piso 2740-244 Porto Salvo Portugal	Relmus	8mg	Orodispersible tablet	Oral use
Spain	TEOFARMA, S.R.L. Vía F Lli Cervi, 8 Valle Slimbene (Pavia) I-27010 Italy	ADALGUR COMPRIMIDOS	2mg 500mg	Tablet	Oral use

Annex II

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions

Overall summary of the scientific evaluation of thiocolchicoside containing medicinal products for systemic use (see Annex I)

Thiocolchicoside (TCC) is a semi-synthetic sulfurated colchicoside derivative with a muscle relaxant pharmacological activity. Muscle relaxants are one of the many treatments currently employed in the management of non-specific low back pain. TCC is indicated for the treatment of painful muscular contractures in different settings. Widely used by prescribers in the concerned Member States (see Annex I), the benefits of TCC containing medicinal products are recognised in clinical practice.

After discontinuation by a Company of a phase I clinical trial with TCC because of new non-clinical findings, the Italian medicines agency (AIFA) requested one of the Marketing Authorisation Holders (MAH) of TCC to further investigate the genotoxic potential of TCC and in particular of its metabolites; the MAH was requested to perform *in vivo* and *in vitro* preclinical studies to address the potential genotoxicity of the metabolites of TCC. The results obtained from one of the metabolites' studies (metabolite SL59.0955, M2) led to concerns: new data on the aneugenic effect of the M2 metabolite of TCC generated from the submitted preclinical studies indicated a signal of genotoxic potential

In view of the above, on 15 February 2013, Italy requested the CHMP, under Article 31 of Directive 2001/83/EC, to assess the above concerns regarding aneuploidy and its impact on the benefit-risk balance for TCC containing medicinal products for systemic use. The CHMP was asked to give its opinion on whether the indication of TCC containing medicinal products should be restricted and/or other regulatory measures should be taken. On 21 February 2013, the CHMP started a referral procedure for TCC containing medicinal products.

Aneuploidy (variation in the number of chromosomes and loss of heterozygosity) is recognised as a potential risk factor for cancer when impacting somatic cells, and teratogenicity, embryo-toxicity/spontaneous abortions and impaired male fertility when impacting germ cells[1]. For the purpose of the review of this risk, the MAHs provided an analysis of this genotoxic potential for each systemic route of administration, together with an analysis of possible risk factors, including relevant criteria such as dose and duration of treatment. The CHMP reviewed all available data from pre-clinical and clinical studies, literature and post-marketing experience on aneuploidy for TCC containing medicinal products for systemic use. A relevant summary is presented hereinafter.

Pre-clinical studies

The preclinical development of TCC was mainly performed during the 1980s, and then complemented in the 1990s to be compliant with the European guidelines on the non-clinical documentation for mixed marketing authorisation applications (CPMP/SWP/799/95) and to investigate a new active metabolite SL18.0740 (M1) identified at that time. Subsequent safety assessments focusing on genotoxic potential were issued in 2001[2] and 2003[3] .
After discontinuation of the above-mentioned phase I clinical trial with TCC, the genotoxic potential of the aglycone metabolite SL59.0955 (M2) was further investigated. New studies were performed in 2011 and 2012 regarding the genotoxicity of the parent compound (TCC), its main circulating metabolite SL18.0740 and the aglycone metabolite SL59.0955.

<u>Genotoxicity data on TCC and its main circulating metabolite SL18.0740 (M1)</u>

Various genetic toxicology studies were conducted on TCC and on its major identified metabolite 3-O-glucuronidated aglycone (SL18.0740), which is the active metabolite.

It was concluded that M1 (SL18.0740) is devoid of mutagenic (gene mutations) and clastogenic (structural chromosome damage) potential, but is able to induce aneuploidy (numerical chromosome damage). However a follow-up study (in vivo micronucleus test) defined a no-effect level of 39.6 mg/kg. This was associated with M1 plasma AUC of 4073 ng.h/mL, which is more than 20 times higher than M1 exposure observed in human after a 8 mg bid oral dose of TCC (175 ng.h/mL at 30 min).

Therefore, on the basis of the above-mentioned available data, the CHMP considered the safety margins and benefit/risk for TCC and SL18.0740 (M1) acceptable.

[1] Parry 2000 & 2002; Kirsch-Volders 2002
[2] Kirkland DJ Et al. 2001
[3] Gouy D., 2003

Genotoxicity data on aglycone metabolite SL59.0955 (M2)

Since no relevant genetic toxicology studies were previously performed with the aglycone metabolite SL59.0955, complementary studies (chromosome damage assays) were performed in order to investigate the genotoxic profile of this metabolite and its ability to induce aneuploidy in nonclinical *in vitro* (up to 600 µg/mL) and *in vivo* (up to 150 mg/kg):

- an *in vitro* micronucleus (MN) test in primary culture of human lymphocytes with the aglycone metabolite (SL59.0955), with centromere staining (Whitwell J., 2012);
- an *in vivo* MN test in rat bone marrow following administration of aglycone metabolite (SL59.0955) by oral route in rats with centromere staining and with a full assessment of exposure to SL59.0955 and to 3-O-glucuronidated aglycone metabolite (SL18.0740) to better assess the threshold of exposure (Wase K., October 2012).

The *in vitro MN test in human lymphocytes* showed that M2 induced micronuclei in cultured human peripheral blood lymphocytes in all treatment conditions. Subsequent mechanistic analysis via the use of fluorescence in situ hybridization (FISH) with pan centromeric DNA probes demonstrated that micronuclei were predominantly generated via an aneugenic (numerical chromosome abnormality) mechanism under all treatment conditions; aneuploidy was clearly confirmed by centromere staining.

Under the assay conditions, the No Observed Adverse Effect Level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) were also considered but while acknowledging that chromosome non disjunction (CND) is the most appropriate end-point to investigate when looking for low-dose effects of spindle poisons, conclusion on the search for threshold doses for aneuploidy induction was not possible to draw.

In the *in vivo MN test in rat bone marrow,* after M2 oral administration once daily for two consecutive days at doses of 25, 50, 70, 100 or 150 mg/kg/d, the rats bone marrow micronucleus test was found negative in males. In females, a positive response was observed at doses of 25, 50, 70 and 100 mg/kg/d based on group mean and individual data. Genotoxic mechanisms, such as aneuploidy, involving cell division and non-DNA targets, are known to occur above a certain threshold of exposure. But no NOAEL for aneugenic effects was identified in rat females (LOEL = 25 mg/kg) and no clear dose related effect was observed because only slight difference in exposure (AUC_{0-24} and C_{max}) with 3-demethylthiocolchicine (SL59.0955) were observed between the different doses in males and females. In addition males and females showed only a slight gender difference in exposure. Hence no safety margin could be calculated. The aneugenic effect was observed at LOEL corresponding to only 1.6 x human Cmax and 4.1 x AUC (8mg bid, Per Os (PO)).

After parenteral use, the plasma concentration of M2 is expected to be much lower as the M2 transformation occurs after oral administration mainly by intestinal metabolism. However, whether the exposure to M2 would be below a threshold of aneugenicity (including a sufficient safety margin) is unknown since M2 has not been analysed in the available clinical kinetic studies.

In conclusion, the results of the above pre-clinical studies showed that M2 (SL59.0955) induced micronuclei *in vitro* and *in vivo,* generated via a predominantly aneugenic mechanism under all treatment conditions. In the two *in vitro* and *in vivo* preclinical studies conducted, the findings (increase in the incidence of micronucleated cells) were observed at concentrations/exposures close to the exposures measured in human at therapeutic doses. The CHMP was therefore of the view that the available data allow to confirm a clear aneugenic effect of the thiocolchicoside metabolite M2 at concentrations which are 4 fold the human exposure in plasma after oral 8 mg TCC treatment bid (recommended dose) and starting from 25 mg/kg dose.The submitted data did not allow establishing a NOEL for aneuploidy, thus not excluding the potential for a human risk.

Clinical Safety

Clinical trials and post marketing spontaneous reports were submitted by the MAHs.

Clinical studies

No cases of cancer, congenital abnormalities, spontaneous abortion and impaired male fertility were retrieved from a review of clinical trials and literature.

Post marketing experience

Postmarketing spontaneous cases were collected based on the reports recorded in two MAHs' global pharmacovigilance databases (cut-off dates of 15 February 2013 and 29 April 2013 respectively).

In the first database, 11 cases secondary to exposure during pregnancy were reported:

- six cases of congenital abnormalities (i.e. one multiple malformations leading to abortion, one pulmonary hypoplasia, one cleft palate, one spina bifida, one Poland's syndrome, one patent ductus arteriosus),
- four cases of spontaneous abortion,
- one case of threat of premature delivery.

Case review reports from 2004 up to 29 April 2013 from the second database reported 23 cases secondary to exposure during pregnancy and / or exposition in utero:

- 20 cases due to exposure during the embryonic period, of which:
    - two cases of teratogenic effects (malformations) associated with exposure in early pregnancy (the first quarter is the period during which the risk is the greatest),
    - four cases resulting in discontinuation of the pregnancy (3 spontaneous abortions and one voluntary abortion not due to medical reason),
    - five cases with a favourable evolution (no effect on the new born),
    - nine cases with an unknown evolution of the pregnancy due to lack of documentation.

- 1 case due to exposure during the foetal period (i.e. a case of foetotoxic effects that resulted in foetal or neonatal type of achieving growth impact, or histological or functional maturation of organs in place (the period during which the greatest risk begins in the second quarter of pregnancy),
- and 2 cases with unknown exposure period:
    - 1 case of teratogenic effects (malformations) associated with exposure in early pregnancy,
    - 1 case with an unknown evolution of the pregnancy due to lack of documentation.

No case was registered for neonatal effects related to exposure occurred in late pregnancy or during childbirth.

The CHMP considers that the clinical evidence within the cases reported by the MAHs concerning the consequences of aneuploidy in humans does not allow drawing definitive conclusions. Aneuploidy is a common characteristic of cancer cells. However it is still controversial if aneuploidy is a contributing cause or merely a consequence of neoplastic transformation. In addition, the lack of evidence for the correlation between the use of TCC and cancer could be due to the difficulty of establishing a causal relationship between the medicine and the effect, which may occur years after intake. In most cases the treatment is for short-term use and not associated with the perception of increased cancer risk for both physicians and patients, therefore a causal relationship between cancer occurrence and treatment is difficult to establish.

The CHMP also noted that the limited number of cases of malformations/embryo-foetal toxicities may be due to the fact that, in most of the Member States, the medicine is contraindicated in pregnancy.

Taking the totality of data into account, the CHMP considered that causality cannot be excluded and that aneuploidy should be considered as a cancer risk factor on theoretical grounds.

The CHMP was therefore of the view that risk minimisation measures (RMMs) should be undertaken in order to address the risks of teratogenicity, embryo-toxicity/spontaneous abortions, impaired male fertility and cancer.

- Firstly, since the TCC metabolite M2 has been shown to be aneugenic at exposure levels close to human therapeutic exposure, the CHMP considered that the dose should be restricted (to 8 mg bid PO and 4 mg bid by IM) and long-term use avoided. In that respect, the CHMP was of the view that the indication in *"Parkinson's disease and drug-induced Parkinsonism with special consideration to neurodyslectic syndrome"* should be removed as this is an indication for chronic use. . The CHMP also considered that the use of TCC should be avoided during puberty (12 to 16-18 years) due to potential risk on fertility. The use of the product should therefore be limited to acute conditions in patients over 16 years old; an updated SmPC with restriction for use and duration therapy was endorsed accordingly. Based on common use in acute settings, other recommendations for the posology were included as the limitation of the treatment

duration to 7 days in case of oral administration and to 5 days in case of IM administration; a reference to the maximum dose allowed was also recommended .Finally a 12 hours interval between 2 consecutive administrations was requested in view of the elimination half-life of the M2 metabolite. The corresponding product information sections were updated accordingly. In addition, the CHMP was of the view that the package size should be restricted according to the new treatment-days scheme recommended (up to 30 tablets or capsules/4 mg pack, up to 14 tablets or capsules/8 mg pack and up to 10 vials/ampoules).

- Teratogenicity is classified as an important identified risk. To address the risks of teratogenicity and embryo-toxicity/spontaneous abortions the CHMP agreed on contraindicating TCC during the entire pregnancy period, during lactation, and in women of childbearing potential not using contraception. Amendments to the warnings and pregnancy and lactation sections of the product information were also endorsed.

- Carcinogenicity and impaired fertility are categorised as important potential risks.Concerning the risk of male infertility: elevated sperm chromosome aneuploidy is known to be associated with male infertility. However, more concern was raised in relation to the potential risk of foetal anomalies due to elevated sperm aneuploidy rather than to the male infertility per se. Given the treatment conditions with TCC (short-term, potentially aneugenic at maximum doses) effects on male fertility will be low and a rapid recover to normal levels can be expected. . An amendment to the product information was agreed to address this concern.

- Lastly, evidence for carcinogenicity of aneugens is limited. A significantly increased cancer risk would in general be dependent on long-term/chronic exposure/dosing with the aneugen. Carcinogenicity is an important potential risk. To address it, the proposed RMM (indication limited to acute conditions, treatment duration limited to seven consecutive days, avoidance of long-term use) were considered appropriate by the CHMP.

The CHMP considered that a Direct healthcare professional communication (DHPC) was needed to inform on the outcome of the present review, including the updated indication, the clinical use for these products (short-term) and to highlight the genotoxic risk. A risk management plan (RMP) will be submitted to national competent authorities in accordance with agreed timelines and periodic safety update reports (PSURs) will be submitted every 3 years. In addition the CHMP reviewed the PSUR frequency for TCC containing medicines for systemic use and requested PSURs to be submitted on a three-yearly basis (instead of a 13-yearly basis as it is currently recommended). Continuous monitoring of any safety signal correlated with aneuploidy (i.e. teratogenicity, embryo-foetal toxicity / spontaneous abortion, impaired male fertility and cancer) and pregnancy reporting to collect structured data on accidental exposure to the drug should be performed. A mock-up of the above-mentioned pregnancy reporting form should be provided in the RMP and a report on these collected data should be submitted within PSURs.

Furthermore the CHMP requested a drug utilisation study (DUS) to be conducted in order to better characterise prescribing practices for these medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription. This DUS should be conducted over a three year period. The study protocol should be provided within the RMP.

Finally educational material for prescribers and for patients highlighting the risks and warnings of genotoxicity reactions will also be submitted to national competent authorities within the RMP.

Benefit –risk balance

Having noted the above, the CHMP concluded that the benefit-risk balance of TCC containing medicinal products indicated as adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards remains favourable subject to the restrictions, warnings, other changes to the product information, additional pharmacovigilance activities and RMMs agreed.

Grounds for the maintenance of the marketing authorisations

Whereas

- The Committee considered the procedure under Article 31 of Directive 2001/83/EC for thiocolchicoside containing medicinal products for systemic use (see annex I).

- The Committee considered all available data from pre-clinical, clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience on the safety of thiocolchicoside containing medicinal products for systemic use with regards to its genotoxicity.

- The Committee considered that thiocolchicoside containing medicinal products for systemic use remain an effective adjuvant treatment of painful muscle contractures in acute spinal pathology. However, having considered the risks, thiocolchicoside containing medicinal products for systemic use should only be administered to patients over 16 years of age in acute conditions, with treatment duration limited to 7 (oral) and 5 (IM) consecutive days. In that respect, the CHMP was of the view that the indication in *"Parkinson's disease and drug-induced Parkinsonism with special consideration to neurodyslectic syndrome"* should be removed as this is a chronic condition which requires longer treatment duration. The package size should be adapted to new recommended treatment-days. .

- The Committee considered also that thiocolchicoside containing medicinal products for systemic use should be contraindicated during the entire pregnancy period. These products should also be contraindicated in women of childbearing potential not using contraception and during lactation. The CHMP also recommended further changes to the product information including information on fertility.

- The CHMP also agreed on the need of a RMP. In addition, three-yearly PSURs should be submitted by all MAHs of these products. These PSURs should include a report compiling continuous monitoring of any safety signal correlated with aneuploidy and pregnancy on accidental exposure to the drug.

- The Committee concluded that there was a need for further risk minimisation measures such as a drug utilisation study to characterise the prescribing practices during typical clinical use, as well as adequate educational materials to be developed for patients and prescribers. These measures are to be included in the RMP.

The Committee, as consequence, concluded that the benefit-risk balance of thiocolchicoside containing medicinal products for systemic use as adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwardsremains favourable, subject to the restrictions, warnings, other changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed.

Annex III

Amendments to relevant sections of the summary of product characteristics, labelling and package leaflets

SUMMARY OF PRODUCT CHARACTERISTICS

[the wording below should be inserted]

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[the currently approved indications should be deleted and replaced by the following]

Adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents from 16 years onwards.

4.2 Posology and method of administration

[the currently approved wording should be deleted and replaced by the following]

Posology
o *For the oral form 4 mg and 8 mg:*
The recommended and maximal dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days.

o *For IM form:*
The recommended and maximal dose is 4 mg every 12 hours (i.e. 8 mg per day). The treatment duration is limited to 5 consecutive days.

o *Both for oral and for IM:*
Doses exceeding recommended doses or long-term use should be avoided (see section 4.4).

Paediatric population
<Invented name> should not be used in children and adolescents under 16 years of age because of safety concerns (see section 5.3).

Method of administration
[To be completed nationally]

4.3 Contraindications

[the wording below should be inserted]

Thiocolchicoside must not be used
- in patients hypersensitive to the active substance or to any of the excipients listed in section 6.1
- during the entire pregnancy period
- during lactation
- in women of childbearing potential not using contraception.

4.4 Special warnings and precautions for use

[the wording below should be inserted]

[...]
Preclinical studies showed that one of thiocolcoside metabolites (SL59.0955) induced aneuploidy (i.e.

unequal number of chromosomes in dividing cells) at concentrations close to human exposure observed at doses 8 mg twice daily per os (see section 5.3). Aneuploidy is considered as a risk factor for teratogenicity, embryo/foeto-toxicity, spontaneous abortion, and impaired male fertility and a potential risk factor for cancer. As a precautionary measure, use of the product at doses exceeding the recommended dose or long-term use should be avoided (see section 4.2).

Patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed.

4.6 Fertility, pregnancy and lactation

[the currently approved wording should be deleted and replaced by the following]

[…]

Pregnancy
There are limited data on the use of thiocolchicoside in pregnant women. Therefore, the potential hazards for the embryo and foetus are unknown.
Studies in animals have shown teratogenic effects (see section 5.3).
<Invented name> is contraindicated during pregnancy and in women of childbearing potential not using contraception (see section 4.3).

Breastfeeding
Since it passes into the mother's milk, the use of thiocolchicoside is contraindicated during breastfeeding (see section 4.3).

Fertility
In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is a risk factor for impairment of human fertility (see section 5.3).

4.8 Undesirable effects

[…]

[the wording below should be inserted]

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

*[*For the printed material, please refer to the guidance of the annotated QRD template.]*
[…]

5. PHARMACOLOGICAL PROPERTIES

5.2 Pharmacokinetic properties

[the currently approved wording should be deleted and replaced by the following]

Absorption
- After IM administration, thiocolchicoside Cmax occur in 30 min and .reach values of 113 ng/mL after a 4 mg dose and 175 ng/mL after a 8 mg dose. The corresponding values of AUC are respectively 283 and 417 ng.h/mL.
The pharmacologically active metabolite SL18.0740 is also observed at lower concentrations with a Cmax of 11.7 ng/mL occurring 5 h post dose and an AUC of 83 ng.h/mL.
No data are available for the inactive metabolite SL59.0955.

- After oral administration, no thiocolchicoside is detected in plasma. Only two metabolites are observed:
The pharmacologically active metabolite SL18.0740 and an inactive metabolite SL59.0955. For both metabolites, maximum plasma concentrations occur 1hour after thiocolchicoside administration. After a single oral dose of 8 mg of thiocolchicoside the Cmax and AUC of SL18.0740 are about 60 ng/mL and 130 ng.h/mL respectively. For SL59.0955 these values are much lower: Cmax around 13 ng/mL and AUC ranging from 15.5 ng.h/mL (until 3h) to 39.7 ng.h/mL (until 24h).
Distribution
The apparent volume of distribution of thiocolchicoside is estimated around 42.7 L after an IM administration of 8 mg. No data are available for both metabolites.
Biotransformation
After oral administration, thiocolchicoside is first metabolized in the aglycon 3-demethyltiocolchicine or SL59.0955. This step mainly occurs by intestinal metabolism explaining the lack of circulating unchanged thiocolchicoside by this route of administration.
SL59.0955 is then glucuroconjugated into SL18.0740 which has equipotent pharmacological activity to thiocolchicoside and thus supports the pharmacological activity after oral administration of thiocolchicoside. SL59.0955 is also demethylated into didemethyl-thiocolchicine.
Elimination
- After IM administration the apparent $t_{1/2}$ of thiocolchicoside is 1.5h and the plasma clearance 19.2 L/h.
- After oral administration, total radioactivity is mainly excreted in feces (79%) while urinary excretion represents only 20%. No unchanged thiocolchicoside is excreted either in urine or feces. SL18.0740 and SL59.0955 are found in urine and feces while the didemethyl-thiocolchicine is only recovered in feces.
After oral administration of thiocolchicoside, the SL18.0740 metabolite is eliminated with an apparent $t_{1/2}$ ranging from 3.2 to 7 hours and the metabolite SL59.0955 has a $t_{1/2}$ averaging 0.8h.

5.3 Preclinical safety data

[the currently approved wording should be deleted and replaced by the following]

Thiocolchicoside profile has been assessed *in vitro,* and *in vivo* following parenteral and oral administration.
Thiocolchicoside was well tolerated following oral administration for periods of up to 6 months in both the rat and the non-human primate when administered at repeated doses of less than or equal to 2 mg/kg/day in the rat and less or equal to 2.5 mg/kg/day in non-human primate, and by the intramuscular route in the primate at repeated doses up to 0.5 mg/kg/day for 4 weeks.
At high doses, thiocolchicoside induced emesis in dog, diarrhoea in rat and convulsions in both rodents and non-rodents after acute administration by oral route.
After repeated administration, thiocolchicoside induced gastro-intestinal disorders (enteritis, emesis) by oral route and emesis by IM route.
Thiocolchicoside itself did not induce gene mutation in bacteria (Ames test), *in vitro* chromosomal damage (chromosome aberration test in human lymphocytes) and *in vivo* chromosomal damage (*in vivo* micronucleus in mouse bone marrow administered intraperitoneally).
The major glucuro-conjugated metabolite SL18.0740 did not induce gene mutation in bacteria (Ames test); however it induced *in vitro* chromosomal damage (*in vitro* micronucleus test on human lymphocytes) and *in vivo* chromosomal damage (*in vivo* micronucleus test in mouse bone marrow administered orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH centromere staining), suggesting aneugenic properties. The aneugenic effect of SL18.0740 was observed at concentrations in the *in vitro* test and at AUC plasma exposures in the *in vivo* test higher (more than 10 fold based on AUC) than those observed in human plasma at therapeutic doses.
The aglycon metabolite (3-demethylthiocolchicine-SL59.0955) formed mainly after oral administration induced *in vitro* chromosomal damage (*in vitro* micronucleus test on human lymphocytes) and *in vivo* chromosomal damage (*in vivo* oral micronucleus test in rat bone marrow administred orally). The micronuclei predominantly resulted from chromosome loss (centromere positive micronuclei after FISH or CREST centromere staining), suggesting aneugenic properties. The aneugenic effect of SL59.0955 was observed at concentrations in the *in vitro* test and at exposures in the *in vivo* test close to those observed in human plasma at therapeutic doses of 8 mg twice daily per os. Aneugenic effect in dividing cells may result in aneuploid cells. Aneuploidy is a modification in the number of chromosomes and loss of heterozygosity, which is recognized as a risk factor for teratogenicity, embryotoxicity/ spontaneous abortion, impaired male fertility, when impacting germ cells and a potential risk factor for cancer when impacting somatic cells. The presence of the aglycon metabolite (3-

demethylthiocolchicine-SL59.0955) after intramuscular administration has never been assessed, therefore its formation using this route of administration can not be excluded.
In the rat, an oral dose of 12 mg/kg/day of thiocolchicoside caused major malformations along with foetotoxicity (retarded growth, embryo death, impairment of sex distribution rate). The dose without toxic effect was 3 mg/kg/day.

In the rabbit, thiocolchicoside showed maternotoxicity starting from 24 mg/kg/day. Furthermore, minor abnormalities have been observed (supernumerary ribs, retarded ossification).

In a fertility study performed in rats, no impairment of fertility was seen at doses up to 12 mg/kg/day, i.e. at dose levels inducing no clinical effect. Thiocolchicoside and its metabolites exert aneugenic activity at different concentration levels, which is recognised as a risk factor for impairment of human fertility.
The carcinogenic potential was not evaluated.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

[the currently approved wording should be deleted and replaced by the following]

30 tablets/capsules for the 4mg dose and 14 tablets/capsules for the 8mg dose.
10 vials/ampoules for the 4 mg/2 ml dose.

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton for capsules, hard /tablets/orodispersible tablets and solution for injection

4. PHARMACEUTICAL FORM AND CONTENTS

[the currently approved wording should be deleted and replaced by the following]

4 mg
[up to 30] hard capsules
[up to 30] tablets

8 mg
[up to 14] hard capsules
[up to14] orodispersible tablets

4 mg/2 ml
[up to 10] vials/ampoules

PACKAGE LEAFLET

[the wording below should be inserted]

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

[…]

PL

Package leaflet: Information for the patient

1. What X is and what it is used for

[the currently approved wording should be deleted and replaced by the following]

This medicine is a muscle relaxant. It is used in adults and adolescents from 16 years onwards as an adjuvant treatment for painful muscular contractions. It is to be used for acute conditions related to spinal column.

2. What you need to know before you take X

[the wording below should be inserted]

Do not take X if:
- you are allergic to thiocolchicoside or any of the other ingredients of this medicine (listed in section 6)
- you are pregnant, might become pregnant or think you may be pregnant
- you are a woman of childbearing potential not using contraception
- you are breast feeding

Warnings and precautions
[…]
Strictly respect the doses and duration of treatment detailed in section 3. You should not use this medicine at higher dose or for longer than 7 days *(for oral forms)*/5 days *(for IM forms).* This is because one of the products formed in your body when taking thiocolchicoside at high doses might cause damage to some cells (abnormal number of chromosomes). This has been shown in studies in animals and in laboratory studies. In humans, this type of damage to cells is a risk factor for cancer, harm to the unborn child, and impairment of male fertility. Please discuss with your doctor if you have further questions.

Your doctor will inform you about all measures relating to an effective contraception and about the potential risk of a pregnancy.

Children and adolescents
Do not give this medicine to children and adolescents below 16 years old because of safety concerns.

Pregnancy, breast-feeding and fertility

[the currently approved wording should be deleted and replaced by the following]

Do not take this medicine if:
- you are pregnant, might become pregnant or think you may be pregnant
- you are a woman of childbearing potential not using contraception

This is because this medicine may harm your unborn child. Do not take this medicine if you are breast-feeding. This is because the medicine passes into your breast-milk.

This medicine might cause problems to the male fertility due to potential damage to sperm cells (abnormal number of chromosomes). This is based on laboratory studies (see section 2 “Warnings and precautions”).

3. How to take X

[the currently approved wording should be deleted and replaced by the following]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
o *For the oral form 4 mg and 8 mg:*
The recommended and maximal dose is 8 mg every 12 hours (i.e. 16 mg per day). The treatment duration is limited to 7 consecutive days.
o *For intramuscular form:*
The recommended and maximal dose is 4 mg every 12 hours (i.e. 8 mg per day). The treatment duration is limited to 5 consecutive days.
o *Both for oral and for intramuscular forms:*
Do not exceed the recommended doses and treatment duration.
This medicine should not be used for long-term treatment (see section 2 “Warnings and precautions”).
Use in children and adolescents
Do not give this medicine to children and adolescents below 16 years old because of safety concerns.
If you take more X than you should
If you accidentally take more X than you should talk to your doctor, pharmacist or nurse.
If you forget to take X
Do not take a double dose to make up for a forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

[This wording should be inserted]

Like all medicines, this medicine can cause side effects, although not everybody gets them.
[…]
[the wording below should be inserted]

> **Reporting of side effects**
> If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via {the national reporting system listed in Appendix V}*. By reporting side effects you can help provide more information on the safety of this medicine.
>
> *[*For the printed material, please refer to the guidance of the annotated QRD template.]*

6. Contents of the pack and other information

[the currently approved wording should be deleted and replaced by the following]

30 tablets/capsules for the 4mg dose and 14 tablets/capsules for the 8mg dose.
10 vials/ampoules for the 4 mg/2 ml dose.

Annex IV

Conditions to the marketing authorisations

Conditions to the marketing authorisation

National competent authorities of Member State(s) coordinated by reference Member State(s) if applicable, shall ensure that the following conditions are fulfilled by the MAH(s):

Conditions	**Date**
The MAHs should circulate the agreed DHPC in coordination with the NCAs according to the action plan agreed by CHMP.	Within 30 days following EC decision
The MAHs should submit a risk management plan (including outline of DUS and educational materials, see also below) in EU format.	Within 2 months following EC decision
Thiocolchicoside takes part in the PSUR synchronisation project of the Heads of Medicine Agencies. The MAH(s) should submit the next PSUR by:	4 July 2015
The MAH(s) should provide within the risk management plan submission, a protocol for the drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription. Final study report by:	November 2017
The MAHs should provide within the risk management plan educational material for prescribers and patients. This will highlight the risks and warnings of genotoxicity reactions.	Within 2 months following EC decision